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Enantioselective Cyclopropanation of Allylic Alcohols Catalyzed by a Chiral Disulfonamide-Aluminum Complex

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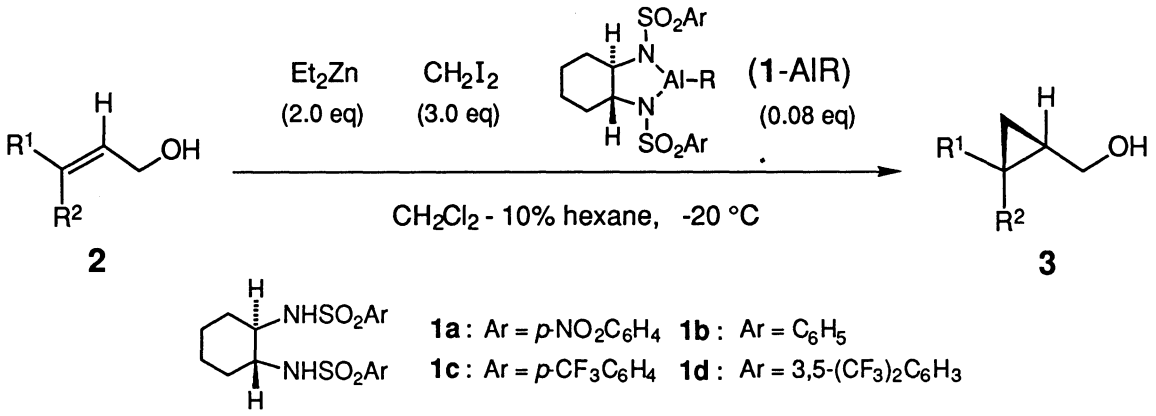
A chiral disulfonamide-alkylaluminum complex prepared from (1*R*,2*R*)-*N*,*N*'-bis(benzenesulfonyl)-1,2-cyclohexanediamine and trialkylaluminum or *i*-Bu_2AlH has been found to catalyze a Simmons-Smith cyclopropanation of allylic alcohols with Et_2Zn and CH_2I_2 to afford the corresponding cyclopropanes in excellent yields with high enantiomeric excesses.

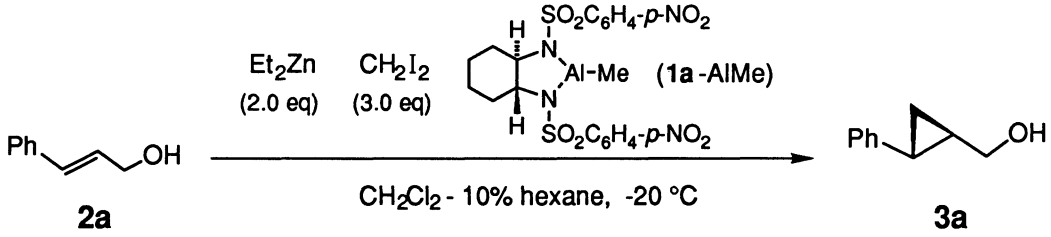
Cyclopropane skeleton is a quite interesting structural unit because it is found in many naturally occurring substances[2] and also in synthetic materials of biological and medicinal importances.[3] Therefore, the development of an enantioselective cyclopropanation has extensively been investigated in these years.[4,5] The first catalytic and enantioselective Simmons-Smith cyclopropanation using a disulfonamide-zinc complex was recently reported in our group.[6a] We have now found that a chiral disulfonamide-alkylaluminum complex also catalyzes the cyclopropanation of allylic alcohols with Et_2Zn and CH_2I_2.



Preliminary experiments were aimed to establish the optimized condition for the preparation of the chiral aluminum complex (Table 1), and effects of the alkyl and substituted benzenesulfonyl moieties of the chiral aluminum complex on enantioselectivity were also examined (Table 2) using (1*R*,2*R*)-*N*,*N*'-bis(arenesulfonyl)-1,2-cyclohexanediamine (**1**) as a chiral controller ligand, aluminum as the Lewis acidic metal component, and cinnamyl alcohol as an allylic alcohol. In these experiments, disulfonamide-aluminum complex (**1**-AlR) was first prepared *in situ* in $ClCH_2CH_2Cl$, and after removal of the solvent *in vacuo*, cyclopropanation was then carried out in CH_2Cl_2 at -20 °C. The complex **1**-AlR definitely accelerated and catalyzed the cyclopropanation of cinnamyl alcohol with Et_2Zn and CH_2I_2. As shown in Table 1, higher

enantiomeric excess was observed when the aluminum complex was prepared by adding a hexane solution of Me_3Al to the solution of the ligand (**1a**) in $ClCH_2CH_2Cl$ at lower temparature (-10-25 °C), followed by heating at 80 °C for 3 h (entries 2, 5, and 6).[7] Furthermore, use of slightly less equivalent of Me_3Al gave better enantioselectivity (entries 5 and 6).

Table 1. Condition for Catalyst (**1a**-AlMe) Preparation

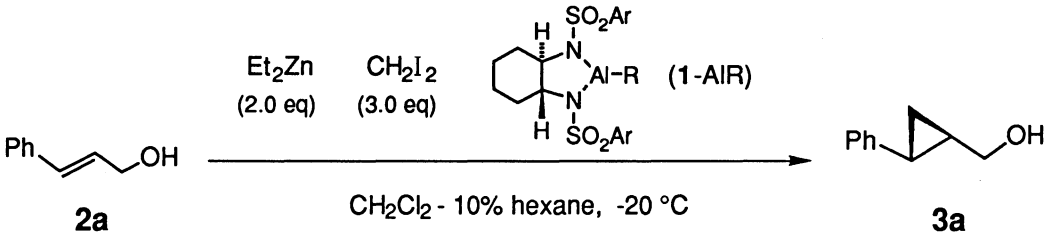


2a **3a**

		Addition	Catalyst formation		Cyclopropanation		
Entry	**1a** : Me_3Al[a]	Temp /°C	Temp /°C	Time /h	Time /h	Yield /%	e.e. /%
1	0.1 : 0.1	25	25	1	20	94	3
2	0.1 : 0.1	25	80	3	20	quant.	62
3	0.1 : 0.1	80	80	3	20	97	28
4	0.1 : 0.2	25	80	3	21	quant.	54
5	0.1 : 0.08	25	80	3	5	quant.	69
6	0.1 : 0.08	-10	80	3	3	quant.	70

a) Equivalent based on cinnamyl alcohol.

Table 2. Effect of R and Ar Moieties of Aluminum Complex **1a**-AlR on Enantioselectivity



2a **3a**

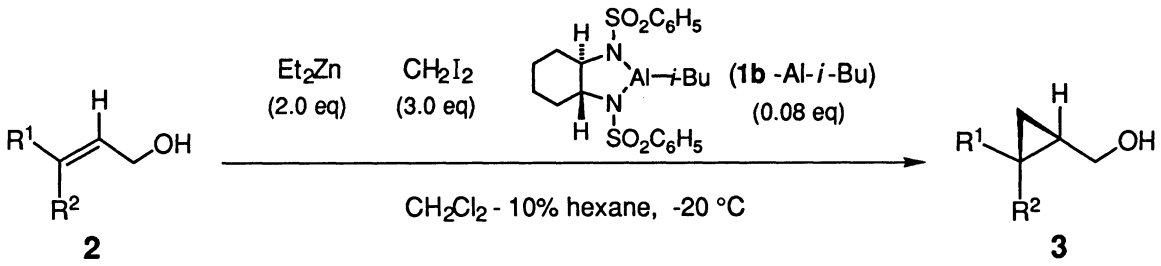
Entry	R	Ar	Time /h	Yield /%	e.e./%
1[a]	Me	CF_3	18	quant.	14
2[a]	Me	*p*-$NO_2C_6H_4$	3	quant.	70
3[a]	Et	*p*-$NO_2C_6H_4$	3	quant.	66
4[a]	*i*-Bu	*p*-$NO_2C_6H_4$	12	quant.	71
5[b]	*i*-Bu	*p*-$NO_2C_6H_4$	12	quant.	73
6[b]	*i*-Bu	*p*-$CF_3C_6H_4$	18	quant.	66
7[b]	*i*-Bu	3,5-$(CF_3)_2C_6H_3$	18	96	17
8[b]	*i*-Bu	C_6H_5	14	quant.	76

a) The catalyst was prepared from **1** (0.05 mmol) and R_3Al (0.04 mmol).
b) The catalyst was prepared from **1** (0.05 mmol) and *i*-Bu_2AlH (0.04 mmol).

The results in Table 2 indicate that (i) the arenesulfonamide group apparently contributes to the construction of an effective chiral environment, (ii) an electron-withdrawing group on the benzene ring is not always necessary for rate enhancement as well as enantioselectivity, (iii) the bulkiness of the alkyl group attached to the central metal does not significantly affect enantioselectivity.

The results of the extensive experiments using **1b**-Al-*i*-Bu prepared from **1b** and diisobutylaluminum hydride (DIBAL) are indicated in Table 3. Enantiomeric excesses of the resulting cyclopropanes were determined by HPLC analysis with chiral column.[6a] The absolute configuration was established to be as shown by measuring $[\alpha]_D$ value and/or the direct comparison on chiral HPLC with the authentic sample.[6a]

Table 3. Cyclopropanation of Allylic Alcohols Catalyzed by **1b**-Al-*i*-Bu[a,b]



Entry	Allylic alcohol 2	R^1	R^2	Concentration mmol/mL	Time /h	Cyclopropane 3	Yield /%	e.e./%
1	**2a**	Ph	H	0.04	14	**3a**	quant.	76
2	**2b**	H	Ph	0.04	6	**3b**	quant.	73
3	**2c**	$PhCH_2CH_2$	H	0.04	6	**3c**	quant.	78
4[c]	**2c**	$PhCH_2CH_2$	H	0.10	6	**3c**	95	79
5	**2d**	$TrOCH_2$	H	0.04	12	**3d**	83	80
6	**2e**	H	$TrOCH_2$	0.04	12	**3e**	92	56
7	**2f**	H	$BnOCH_2$	0.04	26	**3f**	91	26

a) All reactions except for entry 4 were carried out with an allylic alcohol (0.5 mmol), Et_2Zn (1.0 mmol), and CH_2I_2 (1.5 mmol) in CH_2Cl_2 at -20 °C.
b) The catalyst (**1b**-Al-*i*-Bu) was prepared from **1b** (0.1 equiv.) and *i*-Bu_2AlH (0.08 equiv.).
c) Cyclopropanation was carried out in 5 mmol scale.

Although enantioselectivities of the present cyclopropanation are similar to those obtained with the chiral zinc catalyst **1a**-Zn,[6a] the most characteristic feature of the chiral aluminum complex-catalyzed reaction is that no decrease in an enantioselectivity was observed even in a higher concentration (Entry 4).[8]

Furthermore, from a mechanistic point of view, the present study would provide a valuable information for understanding how the chiral sulfonamide-modified Lewis acid participates in the transition state since both aluminum and zinc complex (**1**-AlR and **1**-Zn) afforded the cyclopropanes in a similar enantioselectivities with the same enantioface selection. Investigations along this line as well as the application of this methodology are under way in our laboratory.

A typical procedure is described for the cyclopropanation of (*E*)-5-phenyl-2-penten-1-ol (**2c**): To a colorless clear solution of **1b** (192 mg, 0.488 mmol, 0.1 equiv.) in 25 mL of anhydrous $ClCH_2CH_2Cl$ was added dropwise at 0 °C a solution of DIBAL in hexane (0.93 M, 420 μL, 0.390 mmol, 0.08 equiv.). After being stirred for 30 min at rt and for 3 h at 80 °C, the $ClCH_2CH_2Cl$ was removed *in vacuo*. To the colorless solution of the freshly prepared **1b**-Al-*i*-Bu in 50 mL of anhydrous CH_2Cl_2 were added dropwise at -50 °C a hexane solution of Et_2Zn (0.98 M, 9.76 mL, 9.76 mmol, 2 equiv.), a solution of (*E*)-5-phenyl-2-penten-1-ol (790 mg, 4.88 mmol, 1 equiv.) in 5 mL of CH_2Cl_2, and CH_2I_2 (1.18 mL, 14.6 mmol, 3 equiv.). The mixture was stirred for 6 h at -20 °C, quenched at -20 °C with 3 mL of Et_3N, diluted with 200 mL of Et_2O, washed with 50 mL of brine, and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica gel with a 1:1 mixture of ethyl acetate and hexane to afford (2*R*,3*R*)-2,3-methano-5-phenylpentan-1-ol (**3c**; 817 mg, 95% yield, 79% ee, $[\alpha]_D^{22}$ 24.6° (c 1.1, $CHCl_3$)) as a colorless oil.

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7) E. J. Corey, R. Imwinkelried, S. Pikul, and Y. B. Xiang, *J. Am. Chem. Soc.*, **111**, 5493 (1989).
8) We have observed a siginificant decrease in an enantioselectivity with **1a**-Zn when the cyclopropanation was conducted in a higher concentration (~0.1 mmol/mL). We attribute this to the less solubility of **1a**-Zn. In contrast, the chiral aluminum complex **1b**-Al-*i*-Bu is readily soluble in CH_2Cl_2.

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